REMARKS/ARGUMENTS

Claim 30 has been revised to include the feature of adding L1 and L2 and deleting L39A to the humanized chicken immunoglobulin. Support for the revision is found on page 23, lines 16-24. Claim 30 has also been revised to delete reference to segments to remove any ambiguity of the claim. The revisions are not in acquiescence to any rejection of record. Applicants reserve the right to pursue the subject matter no longer within the scope of the amended claims in a continuing application without prejudice.

Claim 33 has been revised to clearly point out that the amino acid residues being replaced are according to the numbering of Kabat. Support for the revision is found on page 23, line 11.

New claims 34 and 35, dependent from claims 30 and 31 respectively, have been introduced. They are supported at least by claims 1 and 2 as originally filed.

No new matter has been introduced, and entry of the revised claims is respectfully requested to leave claims 30-35 pending.

Formal Matters Regarding Sequence Compliance

The Description of the Figures has been revised to include sequence identifiers, SEQ ID NO. 104 in Figure 1.

Applicants submit a second substitute sequence listing to provide SEQ ID NO. 104. This amendment conforms the sequence listing to the corresponding sequence shown in Fig. 1(B). No new matter is involved.

This amendment is accompanied by a floppy disk containing the above named sequences, SEQ ID NOS: 1-104, in computer readable form, and a paper copy of the sequence information which has been printed from the floppy disk. The information contained in the computer readable disk was prepared through the use of the software program "PatentIn" and is identical to that of the paper copy. This amendment contains no new matter.

Objection to the Specification

The Description of the Drawings is objected because Figures 25 and 26 contain parts A-O and A-B, respectively, that are not described in the Description of the Drawings.

The specification has been revised to include references to parts A-O and A-B in Figures 25 and 26. Support can be found on page 60, lines 14-22, and page 61, lines 10-13, respectively.

The specification has also been revised to provide a new title that is clearly indicative of the invention to which the claims are directed. Applicants thank the Examiner for the suggestion of the new title.

Alleged Rejection Under 35 U.S.C. § 112, Second Paragraph

Claims 30-33 were rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to recitation of the term DNA segments. Applicants respectfully point out that the reference to "segments" has been deleted from the amended claim. The claims as amended are now directed to preparing expression vectors comprising DNA encoding a humanized heavy chain variable region and/or a humanized light chain variable region. As indicated by the Examiner, those of skill in the art recognize that the expressed heavy chain and light chain variable regions are each contiguous sequences of four framework regions (FRs) and three complementarity-determining regions (CDRs) (i.e., FR1-CDR1-FR2-CDR2-FR3-CDR3-FR4). Therefore, Applicants respectfully submit that no issue of indefiniteness or ambiguity exists in the amended claims, and respectfully request that the rejection be withdrawn.

Claim 32 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to insufficient antecedent basis for the limitation "the amino acid of the human acceptor immunoglobulin framework..." Applicants respectfully traverse the rejection. The claim refers to replacing an amino acid of a human acceptor immunoglobulin framework when the replaced amino acid is rare for human immunoglobulin sequences at its position. "Rare", which as used herein, indicates an amino acid occurring at that position in less than about 20% but usually less than about 10% of human heavy or light chain V region sequences in a representative data bank (see page 22, line 34 through page 23, line 2). Such rare framework amino acid of human acceptor immunoglobulin is then replaced by a consensus amino acid,

which is the residue typical for the human sequence (see page 23, lines 2-4). Therefore, Applicants respectfully submit that, in view of the specification, no issue of indefiniteness exists in the claim and, respectfully request that rejection of the claim be withdrawn.

Claim 33 was rejected under 35 U.S.C. § 112, second paragraph, as allegedly indefinite due to lack of reference to the framework amino acid residues. The claim has been revised to specifically point out that the amino acid numbering is according to Kabat. Support for the revision can be found at page 13, lines 26-29, which states that "as used herein, the term "framework region" refers to those portions of immunoglobulin light and heavy chain variable regions that are relatively conserved (i.e., other than the CDRs) among different immunoglobulins in a single species, as defined by Kabat, et al." Therefore, Applicants respectfully submit that, in view of the amendment, no issue of indefiniteness exits in the claim, and, respectfully request that rejection of the claim be withdrawn.

Alleged Rejection Under 35 U.S.C. § 103

Claims 30-33 were rejected under 35 U.S.C. § 103(a) as allegedly unpatentable over Andris-Widhopf et al and Queen et al.

Andris-Widholf et al teach methods for the generation of chimeric chicken immunoglobulins. The Examiner acknowledges that Andris-Widhopf et al do not teach a method of producing a humanized chicken immunoglobulin but alleges that Queen et al teach a method of producing humanized immunoglobulins that are less immunogenic in human patients and better suited for human therapy. The Examiner takes the view that one would have been motivated to modify the chimeric chicken immunoglobulin of Andris-Widhopf et al and produce a humanized chicken immunoglobulin according to the method of Queen et al. Considering the added feature in the amended claims, this rejection is respectfully traversed.

The claims as amended are directed to methods of producing a humanized chicken immunoglobulin, wherein L1 and L2 of the light chain variable region frameworks from the human acceptor immunoglobulin are added to L1 and L2 of the humanized chicken immunoglobulin and L39A of the donor chicken immunoglobulin is deleted in the humanized chicken immunoglobulin, wherein amino acid numbering is according to Kabat.

"Obviousness cannot be established by combining the teachings of the prior art to produce the claimed invention, absent some teaching, suggestion or incentive supporting the combination." *In re Geiger*, 2 USPQ2d 1276 (Fed. Cir. 1987). The motivation must have sufficient "force" to "impel persons skilled in the art to do what applicant has done." *Ex parte Levengood*, 28 USPQ2d 1300, 1302 (BPAI 1993). Here, the alleged motivation is of humanizing a chimeric chicken immunoglobulin according to the method of Queen et al. However, with respect to the amended claims, there is now nothing in the cited references that would have impelled the artisan to produce a humanized chicken immunoglobulin, wherein L1 and L2 of the light chain variable region frameworks from the human acceptor immunoglobulin are added to L1 and L2 of the humanized chicken immunoglobulin and L39A of the donor chicken immunoglobulin is deleted in the humanized chicken immunoglobulin, wherein amino acid numbering is according to Kabat.

Humanization of mouse antibodies has been shown to greatly reduce the immunogenicity in human host. However, humanization of chicken antibodies has its unique technical obstacles compared to humanization of mouse antibodies. First, chicken is more evolutionally distant from human than mouse, so that the difference between chicken and human V genes in amino acid sequence and three dimensional structure is expected to be much larger than that between mouse and human V genes.

Second, chicken light chain V genes, compared to mouse and human light chain V genes, carry two amino acid deletions, L1 and L2, at the N-terminus of mature proteins and one amino acid insertion at L39A in the framework 2. The presence of such deletions/insertions in the chicken light chain V genes makes the prediction of a three dimensional structure of chicken variable regions highly uncertain and unpredictable.

Accordingly, Applicants respectfully submit that no *prima facie* case of obviousness is present because the references do not contain all the claimed features and no adequate motivation to combine the cited references to arrive at the claimed invention, and no reasonable expectation of success in making such a combination, are present. Accordingly this rejection is misplaced and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this Application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, please telephone the undersigned at 650-574-1514.

Respectfully submitted,

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